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Impact of person-centered care training and person-centered activities on quality of life, agitation and antipsychotic use in people with dementia living in nursing homes: A cluster-randomized controlled trial of the WHELD intervention

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Abstract:	Background Agitation is a common, distressing and challenging symptom affecting large numbers of people with dementia and impacting significantly on quality of life (QoL). There is an urgent need for evidence-based, cost-effective psychosocial intervention to improve these outcomes, particularly in the absence of safe, effective pharmacological therapies. This study aimed to conduct a large and rigorous RCT to evaluate the efficacy of a person-centered care and psychosocial intervention (WHELD) on QoL, agitation and antipsychotic use in people with dementia living in nursing homes, and to determine the cost of the intervention. Methods and Findings: This was a randomized controlled cluster trial comparing the

	WHELD intervention with treatment as usual in people with dementia living in 69 UK nursing homes, using an intention to treat analysis. All nursing homes allocated to the WHELD intervention received staff training in person-centered care (PCC), social interaction (SoI) and education regarding antipsychotic medications (AM) followed by ongoing delivery through a care staff champion model. The primary outcome measure was QoL (DEMQOL-proxy). Key secondary outcomes were agitation (Cohen Mansfield Agitation Inventory), neuropsychiatric symptoms (NPI) and antipsychotic use. Other secondary outcome measures were global deterioration (CDR), mood (Cornell Scale for Depression in Dementia CSSD), unmet needs (Camberwell Assessment of Need in the Elderly -CANE), mortality, quality of interactions (Quality of Interactions Scale -QUIS), pain (Abbey pain scale) and cost. Intervention costs were calculated using published cost function figures and compared with usual costs. 847 people were randomized to WHELD or treatment as usual, of whom 553 completed the nine month RCT. The WHELD intervention conferred a statistically significant improvement in QoL compared to treatment as usual over nine months (DEMQOL proxy z score 2.82, p=0.0042, Mean Difference 2.54 SEM 0.88, 95% Confidence Intervals (CI) 0.81, 4.28, Cohen's D 0.24). There was also statisticallya significant benefits in agitation (CMAI Z score 2.68 p=0.0076, Mean Difference 4.27 SEM 1.59, 95% CI -7.39, -1.15, Cohen's D 0.23) and in overall neuropsychiatric symptoms (Z score 3.52 Mean Difference 4.55 SEM 1.28 p=0.00045, 95% CI -7.07,-2.02, Cohen's D 0.30). The benefits were greatest in people with moderate-moderately severe dementia. There was also a statistically significant benefit in positive care interactions as measured by QUIS (19.7% increase, SEM 8.94, 95% CI 2.12, 37.16, Cohen's D 0.55, P=0.03). There were no statistically significant differences between the WHELD intervention and treatment as usual for the other secondary outcomes. A sensitivity analysis using a pre-specified imputation model confirmed statistically significant benefits in DEMQOL proxy, and CMAI and NPI with the WHELD intervention compared to treatment as usual. Antipsychotic drug prescribing was at a low stable level in both treatment groups across the study and the WHELD treatment intervention did not reduce antipsychotic use. The WHELD intervention reduced cost compared to treatment as usual, and the benefits achieved were therefore associated with a cost saving. The main limitation was that antipsychotic review was based on augmenting processes within care homes to trigger medical review and did not in this study involve proactive primary care education. The high mortality rate leading to non-completion in a significant proportion of participants leads to interpretation challenges for this study and for all long term intervention studies in nursing homes. Conclusions These findings suggest that this staff training and non-pharmacological intervention for people with dementia living in nursing homes may be able to achieve benefits to QoL, agitation and neuropsychiatric symptoms, as well as cost saving in a model that can readily be implemented into nursing homes. The benefits in QoL, agitation and neuropsychiatric symptoms had a small effect size. The benefits to agitation and neuropsychiatric symptoms are comparable to (agitation) or better than (NPI) the benefits seen with antipsychotic drugs. Importantly, the benefits were achieved in the context of a cost saving and used a model that can readily be implemented into nursing homes.
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Impact of person-centered care training and person-centered activities on quality of life, agitation and antipsychotic use in people with dementia living in nursing homes: A cluster-randomized controlled trial

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Abstract

Background Agitation is a common, challenging symptom affecting large numbers of people with dementia and impacting on quality of life (QoL). There is an urgent need for evidence-based, cost-effective psychosocial interventions to improve these outcomes, particularly in the absence of safe, effective pharmacological therapies. This study aimed evaluate the efficacy of a person-centered care and psychosocial intervention (WHELD) on QoL, agitation and antipsychotic use in people with dementia living in nursing homes, and to determine its cost.

Methods and Findings: This was a randomized controlled cluster trial conducted between 1st January 2013 and 30th September 2015 which compared the WHELD intervention with treatment as usual in people with dementia living in 69 UK nursing homes, using an intention to treat analysis. All nursing homes allocated to the intervention received staff training in person-centered care (PCC), social interaction (SoI) and education regarding antipsychotic medications (AM) followed by ongoing delivery through a care staff champion model. Primary outcome measure was QoL (DEMQOL-proxy). Secondary outcomes were agitation (Cohen Mansfield Agitation Inventory), neuropsychiatric symptoms (NPI), antipsychotic use, global deterioration (CDR), mood (Cornell Scale for Depression in Dementia CSSD), unmet needs (Camberwell Assessment of Need in the Elderly CANE), mortality, quality of interactions (Quality of Interactions Scale –QUIS), pain (Abbey) and cost. Costs were calculated using cost function figures compared with usual costs. 847 people were randomized to WHELD or treatment as usual, of whom 553 completed the nine-month RCT. The intervention conferred a statistically significant improvement in QoL (DEMQOL proxy z score 2.82, p=0.0042, Mean Difference 2.54 SEM 0.88, 95% Confidence Intervals (CI) 0.81, 4.28, Cohen's D Effect Size 0.24). There were also statistically significant benefits in agitation (CMAI Z score 2.68

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Conclusions

These findings suggest that the WHELD intervention confers benefits to QoL, agitation and neuropsychiatric symptoms, albeit with relatively small effect sizes, as well as cost saving in a model that can readily be implemented into nursing homes. Future work should consider how to facilitate sustainability of the intervention in these settings.

Trial Registration: ISRCTN62237498

Author Summary

Why was this study done?

- People with dementia living in care homes often experience agitation and other symptoms which are difficult to treat and distressing for the individual.

What did the researchers do and find?

- We tested the WHELD programme, which combined staff training, social interaction and guidance on use of antipsychotic medications, in 69 UK care homes in a none-month clinical trial.
- We showed that care homes receiving the WHELD programme saw improvements in quality of life as well as other important symptoms including agitation, behavior and pain in people with dementia.
- The WHELD programme was also shown to be cost-effective.

What do these findings mean?

- The findings show that the WHELD approach is beneficial for people with dementia living in care homes
- WHELD could be provided in an affordable way to improve the lives of these individuals, who often do not receive the care they need.

Introduction

There are 46.8 million people with dementia worldwide, many of whom reside in nursing homes. In the UK one third of people with dementia live in care homes [1] and in the US 64% of people receiving Medicare in nursing homes have dementia [2], demonstrating the international impact of the condition. The majority of these individuals have moderate or severe dementia and have highly complex care needs resulting from a combination of cognitive, functional and communication impairments, neuropsychiatric symptoms and medical comorbidity, all of which combine to impact on quality of life (QoL). Interventions to promote QoL in dementia are limited in the literature, and few trials have examined impact on this important outcome. Despite the close link to agitation and other neuropsychiatric symptoms, risk of falls, worsening cognition and mortality, none of the 18 randomised controlled trials of antipsychotic medication have measured QoL as an outcome [3,4]. There is considerable potential for non-drug approaches to address major drivers of QoL, and a recent systematic review particularly highlighted the benefit conferred by social interaction and pleasant activities on both agitation and antipsychotic use [5]. To date interventions to promote person-centered care have not achieved a significant improvement in QoL for people with dementia [6-8]. The exception is a recently published intensive proof-of-concept study which confrmed the added benefits of combining person-centred care training for care staff, antipsychotic review and social interaction (the WHELD intervention) and demonstrated significant benefits in QoL, as well as a significant reduction in antipsychotic use [9].

Neuropsychiatric symptoms affect 90% of people at some point during the course of their condition [10]. Agitation, frequently including aggression, is particularly common amongst those with moderate to severe dementia living in nursing homes, where the cross-sectional prevalence of these symptoms exceeds 50% [11]. Agitation is associated with increased

distress to residents and a burden to family and professional caregivers [4] and is one of the most challenging symptoms for clinical management. Importantly, agitation is closely associated with reduced QoL in people with dementia. There is evidence to support modest benefits of antipsychotic treatment for some symptoms of agitation, particularly risperidone, olanzapine and aripiprazole for the short-term management of severe aggression. The benefits on other symptoms of agitation and with longer term treatment are less clear [12-15]. Moreover, antipsychotics are associated with severe safety concerns including increased cognitive decline, stroke and death, particularly when used in the long term [13,15-17]. Best practice guidance emphasises the importance of frequent monitoring and judicious prescribing in order to reduce these risks, but also to ensure identification of situations where antipsychotic use is warranted [18,19]. Recent studies also highlight emerging pharmacological alternatives to antipsychotic medications. The CitAD trial examined treatment with citalopram for nine weeks in 186 people with AD, reporting significant reduction in agitation (Odds Ratio 2.13, p=0.01) and caregiver distress [20], and a trial of dextromethorphan-quinidine in 194 people with AD reported clinically relevant benefit to agitation (ordinary least squares z statistic: -3.95, p<0.001) over a ten week treatment period [21]. Whilst this emerging evidence base is promising, there were safety concerns with citalopram and both studies only evaluated relatively short term therapy over 10 weeks. There is also currently a lack of evidence supporting sustained benefit for any current pharmacological treatment for agitation.

Livingston and colleagues (22) in a comprehensive sytematic review examined the benefits of a range of sensory, psychological and behavioural interventions in the treatment of agitation. The authors identified 160 clinical trials and reported promising indications of benefit across

a range of interventions. A parallel systematic review concentrating specifically on psychological and behavioural interventions identified 40 clinical trials in people with dementia, highlighting in particular the potential value of enjoyable acitivites as a successful treatment approach for agitation (5). A more specifc systematic review and meta-analysis concentrating on parallel group clinical trials of dementia related person centred care training identified 5 trials. A meta-analysis of these studies demonstrated significant benefits in the treatment of agitation and in achieving reductions in the use of antipsychotic medications. No significant benefits in improving quality of life were however achieved (8). This literature highlights the growing evidence-base to support the value of person-centered care and non-pharmacological interventions for the management of agitation and reduction in antipsychotic use for people with dementia in nursing homes, which was further augmented by a recently published WHELD factorial intervention [6-8,22-24].

Cost is a major consideration in the development and implementation of interventions in nursing homes [5,8,9,22,23]. None of the evidence-based interventions to promote PCC have been widely adopted in clinical and care practice, and this is likely due in part to a lack of robust evidence regarding the cost profile of these approaches. A potentially cost-effective, practical means of overcoming this issue is to deliver interventions through a Champions model, enabling care staff to take ownership for ongoing implementation in the home, with more limited supervision from external therapists.

The goal of this RCT is to evaluate the impact of the WHELD intervention on QoL, agitation, neuropsychiatric symptoms, antipsychotic reduction and cost in comparison to treatment as usual.

Methods

Study design

This study was a nine month cluster-randomized controlled two-arm trial conducted in 69 UK nursing homes between 1st January 2013 and 30th September 2015. There were three recruiting hubs based in South London, North London and Buckinghamshire. Each cluster was randomized to receive either the WHELD intervention or treatment as usual for nine months. This research was reviewed and approved by the Oxford C National Research Ethics Committee (Ref: 13/SC/0281). This study is registered with the ISRCTN database (Ref: ISRCTN62237498). The full protocol is available in the published protocol paper [25].

Eligibility criteria

Eligible nursing homes had at least 60% of residents with dementia. Nursing homes were excluded if they were receiving special support from their local authority or if they failed to meet the five Care Quality Commission care home quality standards. Within each participating nursing home all residents were considered potentially eligible for inclusion if they met criteria for dementia (defined as a score '1' or greater on the CDR [26], operationalized to require a minimum level of cognitive, functional and neuropsychiatric features).

Interventions

The WHELD intervention consisted of a combination of elements taken from the interventions evaluated in a previous proof-of-concept study [9]. The intervention focused on training in

person-centered care for care staff and on promoting tailored person-centered activities and social interactions. The intervention also involved the development of a system for triggering appropriate review of antipsychotic medications by the prescribing physician attached to each home.

Training for staff was provided by a research therapist. Two lead care staff members (WHELD Champions) were nominated in each care home. These individuals received additional training over a period of four months (one training day per month) with further coaching, supervision and regular review with the therapist over the nine-month period. The WHELD Champions were responsible for the delivery and dissemination of the intervention in each care home. In addition, prescribing physicians were provided with educational materials about the intervention. The control group received treatment as usual (TAU). The WHELD intervention is described in more detail in Box 1 and supplementary table 1.

Box 1 Details of WHELD intervention

ORIENTATION PHASE
Duration: 2 whole days or 4 half days in each home over 1 month
Delivered by : 1 full time WHELD therapist for each 9 care homes
Participants: WHELD Therapist meeting with care home managers, staff teams, Dementia Champions, residents
Aim: For WHELD therapist to meet residents and staff to introduce the project and provide information arsing since the launch event, meet nominated Dementia Champions understand staff hopes and concerns, the layout and facilities of the home where the intervention will take place.

INTERVENTION DELIVERY PHASE

Duration: 8 months (months 2-9)

Months 2-5: 1 day (6 hours) per month for each care home. Training delivered to dementia champions off-site from the care home where they work.

Delivered by: WHELD Therapist

Participants: Dementia Champions from care homes

Aims:

Day 1: Understanding what person centred care (PCC) is and how homes can apply this in the care of residents. Developing ways to share this information with colleagues within the home

Day 2: Writing strengths based Care Plans and providing tailored structured social activities which recognise people's abilities and interests with aim of providing 60 minutes per week per person.

Day 3:Understanding the evidence about the use of antipsychotic medication and familiarisation with best practice guidelines and considering ways homes could work with their local GPs to use this

Day 4: Developing ways to understand the individual needs of people who are distressed (sometimes referred to as "challenging behaviour") using a formulation of need based model and identifying ways of using information gained through PCC/ care planning (sessions 1 and 2) to meet the needs.

Delivery Style :All sessions were manualised and involved: didactic sessions, experiential learning, individual goal setting for each home for dissemination of training information and implementation activities between training sessions

Months 6-9: On –site consultation sessions totalling 8 hours per month with each care home. Delivered flexibly, by negotiation, to best support each homes' needs.

CONCURRENTLY

Months 2-9: Cascade training and implementation of activities

Training Delivered by: Dementia Champions

Activities developed by: Dementia Champions and staff team members

Delivery Style: Adapted for care setting involved standalone training sessions, modelling skills, incorporating sessions into daily routine, working with individual residents to develop personalised and tailored activities for 60 minutes a week , care home team formulation and medication review and goal planning sessions to influence care planning.

Outcome Measures

All participants were assessed for dementia severity at baseline using the CDR [26], a validated scale used to quantify the severity of dementia using a structured interview, and the Functional Assessment Staging Tool (FAST) [27], a validated functional ordinal assessment scale of elderly people with dementia.

All outcome measures were assessed prior to randomization and after nine months of the intervention by a trained research assistant. The assessments at follow-up were collected by research assistants who had not previously visited the participating care homes. The research assistants were blind to treatment allocation, and every effort was made to maintain the blind by minimizing contact between the research assistants and research therapists, ensuring that dementia champions were not informants and clear instructions to care homes and the research team to not disclose treatment allocation. The primary outcome was QoL, measured by the DEMQOL proxy [28], a 31-item interviewer-administered questionnaire answered by a caregiver with a score range of 31 to 124 which assesses the QoL for people with dementia.

The secondary outcome measures were agitation and other neuropsychiatric symptoms, assessed using the Cohen-Mansfield Agitation Inventory (CMAI) [29], a caregiver questionnaire of agitation completed through an interview with the caregiver, consisting of 29 items, each of which is rated on a seven-point scale of frequency. Information regarding antipsychotic use and the use of other psychotropic medications was recorded from medication charts. Overall neuropsychiatric symptoms were assessed with the Neuropsychiatric Inventory (NPI – nursing home version) The NPI-NH [30,31] was developed to assess psychopathology in patients with dementia in nursing homes and evaluates 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behaviour, night-time behaviour disturbances, and appetite and eating abnormalities. The score of each item, if present, represents the product of symptom frequency and severity, with a maximum score of 12 for each domain. Secondary outcomes also included global deterioration (CDR)[26], mood (Cornell Scale for Depression in Dementia CSSD) [32], antipsychotic use, unmet needs (Camberwell Assessment of Need in the Elderly –CANE)[33], quality of interactions (Quality of Interactions Scale –QUIS)[34], pain (Abbey Pain Scale)[35], mortality and cost.

Economic data for each individual in the study were collected using an adapted version of the Client Service Receipt Inventory (CSRI) [36,37] which includes questions about the individual's sociodemographic profile, care home charges, and use of health and social care services. In addition, the staffing inputs of the optimized intervention were measured and covered time spent by the therapist and champion in training, supervision and preparation.

Randomization and Blinding

Nursing homes were allocated to receive either the WHELD intervention or treatment as usual (TAU) using secure web access to the remote randomization centre at North Wales Organization for Randomized Trials in Health Clinical Trial Unit (NWORTH CTU) at Bangor University. Randomization was performed by dynamic allocation [38] to protect against subversion while ensuring that the trial maintained a good balance to the allocation ratio of 1:1 both within each stratification variable and across the trial. Nursing homes were stratified by region and size. The system has been coded and validated in the R statistical package. The NWORTH CTU generated randomization codes and assigned clusters to intervention groups. This information was passed to the trial manager, and only passed on to the PI for each site once all baseline evaluations had been completed.

Individual baseline participants were consented and evaluated prior to randomization to minimize bias. Written consent was provided by participants when the individual had mental capacity to provide consent for their own participation. Written consent was provided by next of kin when individuals did not have mental capacity to consent for themselves. Clinicians and research assistants completing follow-up assessments were blind to treatment allocation. Every attempt was made to minimize accidental un-blinding by minimizing contact between therapists and the researchers collecting outcome data and with clear instructions to researchers and nursing home staff to not discuss treatment allocation.

Sample size

The target minimum sample size was 640 at the nine-month time point. Previous studies indicate that intra-home correlation coefficients rarely exceed 0.05. Taking this into account,

297 a sample size of 640 participants therefore gives 90% power using a significance level of 5%
298 to detect a standardized effect size of 0.3 SDs, which is generally accepted as the lowest
299 threshold of a clinically meaningful benefit. The recruitment of a minimum of 840 participants
300 allowed for loss of 200 through mortality or withdrawal, an important consideration in the
301 context of the high morbidity and mortality of this group.
302
303 *Data Analysis*
304 Outcome measures for the study were assessed at baseline and at nine months. All the
305 outcome measures collected were described and reported using appropriate descriptive
306 statistics and tabular and graphical techniques. Means with 95% confidence intervals were
307 quoted and a 5% significance level was reported. The Consolidated Standards of Reporting
308 Trials (CONSORT) diagram information is presented in order to identify any differential
309 dropout between the arms of the trial. The analysis of the quantitative outcomes was
310 undertaken using a multilevel analysis of covariance (ANCOVA).
311
312 The primary outcome measure (DEMQOL proxy) and the secondary outcome measures were
313 analysed using the multilevel modelling approach to ANCOVA, with the value at nine months
314 as the response. The baseline value was the covariate. The key factor was group (treatment
315 (WHELD or control –Treatment as Usual). The multilevel nature of the design was represented
316 by two levels: care home and individual residents in the care home. Other covariates were
317 number of residents in each cluster and the age, gender and severity of dementia (FAST stage
318 –baseline and follow-up) of participants with dementia. The provisional analysis plan was
319 developed based on the analysis model developed for a previous smaller factorial study of
320 the WHELD intervention (9). In addition to the standard ANCOVA model, this included work

to model and identify the best model for the inclusion of baseline co-variates and evaluation of several imputation models. The same baseline covariate model was used in the final analysis plan for the current study. The imputation model was less predictive in validation analyses than it had been in the factorial study. The completer analysis was therefore analysed as the primary outcome in place of the imputation analysis. Therefore the primary analysis included all participants with data available at the nine month assessment point, and the imputation model was used as a sensitivity analyses. The analysis model was finalized prior to the locking of the study database for the current trial.

The same approach was used for the analysis of all secondary outcomes other than mortality, antipsychotic use, QUIS and cost. CMAI and antipsychotic use, except that baseline CMAI and baseline antipsychotic use were used as covariates rather than baseline DEMQOL proxy.

Mortality and antipsychotic use were compared between treatment groups using Relative Risk with 95% CI. QUIS used care home level data, and was compared between treatment groups using ANCOVA, but because of the smaller sample size did not use baseline covariates.

Further exploratory sub-group analysis were undertaken evaluating differences between WHELD and treatment as usual in people with mild-moderate, moderately severe and severe dementia respectively based on the recommendations of the reviewers as part of the journal submission process. Based on these recommendations effect sizes and Number Needed to Treat were also evaluated.

Cost analysis

Total costs for each participant were derived from the collection of service use data for the three month period prior to the intervention (baseline) and the nine months of the intervention (follow-up) and consisted of three main cost categories: intervention costs, accommodation charges and health and social care costs. Intervention costs were calculated by deriving average hourly costs for WHELD Champions and therapists, combined with time spent by each staff type on training, supervision and intervention delivery, and defined as a per participant cost. An additional cost was defined for the AR element intervention for participants receiving antipsychotics. Accommodation costs were collected as weekly charges for each nursing home. Where this was unavailable or not known the typical charge for a resident with similar level of need to the participant in the study was obtained. Total health and social care costs consisted of services that are the main contributors to the cost of care in nursing homes: hospital inpatient, outpatient, day hospital, accident and emergency services, primary care (calculated as per minute unit costs for GPs and Practice Nurses), community health care and ambulatory care. Data on each nursing home resident's use of health care (obtained from the CSRI) were multiplied by appropriate unit costs to calculate health and social care costs for each participant at each time point. Mean differences in costs and 95% CIs were obtained by non-parametric bootstrapped regression (1000 repetitions) modeling to account for non-normal distributions. A multilevel mixed model was used, controlling for site and age at entry into the study. The adjusted total health and social care cost and outcomes models also included the treatment variable as a random effect at the care home level. Clustering was accounted for by allowing the model intercept and treatment variable coefficient (i.e. treatment effect) to vary by care home.

Sensitivity Analysis

As a sensitivity analysis, the same analysis was undertaken for the primary and key secondary outcomes but using imputed values for people who did not complete the nine month follow-up. Logistic regression was used to predict missing variables from the factors and covariates measured at baseline, using the approach validated in a previous factorial study [39].

Data deposited in the Dryad repository: http://dx.doi.org/10.5061/dryad.j512f21p[40].

Results

Cohort characteristics

1006 participants were consented to the study, with 847 individuals randomized to TAU or WHELD. The majority of participants had moderately severe or severe dementia and 71% were female. Follow-up assessments were available for 553 participants. Mortality accounted for the majority of participants who did not complete follow up assessments. The descriptive statistics for participants who completed the follow up were similar to the original population, although numerically marginally more residents receiving TAU completed the follow up compared to those on WHELD intervention (66.8% vs. 63.6%). The baseline characteristics of the study participants are described in Table 1 and flow of participants through the study is presented in Figure 1. The trial ended after the last follow-up assessment of the last participant was completed.

Table 1 Descriptive statistics for baseline cohort and completers

	Baseline cohort (n = 847)		Completers (n = 553)	
	TAU	**WHELD**	**TAU**	**WHELD**
Total N (%)	443 (100)	404 (100)	296 (66.82)	257 (63.61)
Sex				
Male N (%)	129 (29.1)	132 (32.7)	84 (28.4)	78 (30.4)
Female N (%)	314 (70.9)	272 (67.3)	212 (71.6)	179 (69.6)
Age (Mean, SEM)	88,5 (0.50)	88,4 (0.57)	86.6 (0.50)	86.6 (0.53)
FAST Score				
Mild dementia or less N (%)	35 (7.90)	47 (11.64)	21 (7.09)	23 (8.95)
Moderate dementia N (%)	38 (8.58)	39 (9.65)	15 (5.07)	16 (6.22)
Moderately severe dementia N (%)	267 (60.27)	241 (59.65)	159 (53.71)	153 (59.53)
Severe dementia (N (%)	103 (23.23)	77 (19.06)	101 (34.12)	65 (25.29)
Antipsychotic Use				
Yes N (%)	78 (9.2%)	75 (8.9%)	51 (9.2%)	52 (9.4%)
DEMQOL-Proxy score Mean (SEM)	103.84 (0.70)	103.04 (0.74)	103.69 (0.68)	105.62 (0.59)
CMAI Mean (SEM)	48.49 (1.03)	48.29 (1.04)	48.1 (1.06)	46.0 (1.01)
NPI Mean (SEM)	2.13 (0.13)	2.36 (0.23)	2.14 (0.14)	2.33 (0.24)

393 TAU – Treatment As Usual; FAST – Functional Assessment Staging; DEMQOL – Dementia
394 Quality of Life Scale; CMAI – Cohen-Mansfield Agitation Inventory; NPI – Neuropsychiatric
395 Inventory; SEM – Standard Error of Mean

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397 **Figure 1 CONSORT Chart showing flow of participants through the study**

Outcome Measures

The WHELD intervention conferred a statistically significant 2.54 (SEM 0.88) point improvement in QoL compared to TAU (95% Confidence Intervals (CI) 0.81, 4.28, Cohen's D 0.24).as measured by the DEMQOL-proxy compared to TAU over nine months (z score 2.82, Mean Difference 2.54 SEM 0.88 p=0.0042). On the secondary outcomes, WHELD also conferred a statistically significant 4.27 (95% CI -7.39, -1.15, Cohen's D 0.23, Z score 2.68 Mean Difference 4.27 SEM 1.59 p=0.0076) point benefit on the CMAI compared to TAU with respect to agitation and conferred a statistically significant 4.55 (95% CI -7.07,-2.02, Cohen's D 0.30 , Z score 3.52 Mean Difference 4.55 SEM 1.28 p=0.00045) point benefit on the total NPI NH compared to TAU with respect to overall neuropsychiatric symptoms. The multilevel mixed-effects linear or logistic regression models for primary and secondary outcome measures are shown in Table 2.

Table 2 Effect estimates of WHELD intervention in comparison to TAU on primary outcome and key secondary outcome measures (Multiple Imputation Analysis)

Outcome Measure	**Adj. Effect (SE)***	**p**	Mean Difference (SEM)	95% Confidence Intervals of mean difference	Effect Size (Cohen's D)	Number Needed to Treat$^{\Delta}$
DEMQOL-Proxy (n=553)	R=0.12 Z=2.82	0.0042	2.54^{+} (0.88)	0.81, 4.28	0.24	9
CMAI (n=553)	R – 0.11 Z = 2.68	0.0076	4.27^{+} (1.59)	-7.39, -1.15	0.23	6
NPI (n=547)	R=-1.5 Z=3.52	0.00045	4.55^{+} (1.28	-7.07,-2.02	0.30	9

[*]Adj. effect takes into account baseline value, age, sex, CDR, site, and clustering within care homes.

[Δ] based on binary outcome: better than mean overall outcome or mean outcome or worse than overall mean outcome for DEMQOL and CMAI respectively

[+] DemQOL (Dementia Quality of Life Scale): Improvement in WHELD group from baseline to 9 months 4.78, Improvement in DEMQOL in treatment as usual group 2.24, mean difference 2.54

[+] CMAI (Cohen-Mansfield Agitation Inventory): Improvement in WHELD group from baseline to 9 months -4.13, worsening in CMAI in treatment as usual group 0.14, mean difference 4.27

[+] NPI NH (Neuropsychiatric Inventory, Nursing Home version): Improvement in WHELD group from baseline to 9 months -2.64, worsening in NPI NH in treatment as usual group 1.91, mean difference 4.55

Prescriptions of antipsychotic medications were stable across the study in both treatment groups, with no reduction in prescribing in the WHELD treatment group compared to treatment as usual (Change in Antipsychotic Prescribing: WHELD -0.1% SEM 0.1 , TAU -0.2% SEM 0.1, P=0.60; antipsychotic prescribing at nine months: WHELD v TAU Relative Risk 1.06, 95% CI 0.62 to 1.82 P=0.82). For other secondary outcomes, there were no statistically significant differences between the WHELD group and TAU groups for change in global deterioration (CDR Z= 0.053 Mean Difference 0.011 SEM 0.22 p=0.96), unmet needs (CANE Z=0.84 Mean Difference 0.04 SEM 0.08 P=0.62), pain (Abbey Z=1.084 Mean Difference 0.33 SEM 0.31 p=0.27) or mood (CSSD Z=0.036 mean difference 0.017 SEM 0.48 p=0.97). There

were no significant interaction effects in the primary analysis model, and further analyses accounting for interactions were therefore not undertaken.

The quality of interactions of positive care between care staff and residents with dementia (QUIS) was collected as a care home level assessment in 62 of the participating care homes. There was a statistically significant 19.7% increase in the proportion of positive care interactions (SEM 8.94, 95% CI 2.12, 37.16, Cohen's D 0.55, P=0.03).

A sub-group analysis was also undertaken comparing the WHELD intervention in people with mild-moderate (FAST 4-5), moderately severe (FAST 6) and severe (FAST 7) dementia respectively focusing on the primary and key secondary outcomes (DEMQOL, CMAI, NPI). Statistically significant benefits of similar magnitude to the overall benefits were seen in people with moderately severe dementia for both quality of life, agitation and overall neuropsychiatric symptoms, but there were no statistically significant benefits on quality of life in the smaller groups of individuals with mild-moderate or severe dementia. The full results are shown in Table 3.

Table 3 Effect estimates of WHELD intervention in comparison to TAU on key outcome measures (Multiple Imputation Analysis): Sub-analysis Evaluating impact of WHELD in mild-moderate, moderately severe and severe dementia

	Adj. Effect (SE)*	p	Mean Difference (SEM)	95% Confidence Intervals of mean difference

DEMQOL Proxy				
Severe AD	R=0.00 Z=0.03	0.97	-0.06 (1.72)	(-3.43,3.32)
modsevAD	R=0.20 Z=3.62	0.0003	4.28 (1.16)	(2.01,6.56)
mildmodAD	R=0.06 Z=0.61	0.54	1.11(1.83)	(-2.47,4.69)
CMAI				
severeAD	R=-0.06 Z=0.55	0.58	-2.24 (4.05)	(-10.17,5.69)
modsevAD	R=-0.12 Z=2.08	0.04	-4.52 (2.17)	(-8.77,-0.27)
mildmodAD	R=-0.18 Z=1.93	0.05	-4.57 (2.34)	(-9.15,0.008)
NPI				
Severedem	R=0.19 Z=1.91	0.05	-5.73(2.90)	(-11.42,-0.04)
ModSevdem	R=0.15 Z=2.74	0.006	-4.83(1.75)	(-8.26,-1.387)
MildModdem	R=0.14 Z=1.54	0.13	-3.05(1.99)	(-6.94,0.84)

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461 *Adj. effect takes into account baseline value, age, sex, CDR, site, and clustering within care

462 homes.

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The sensitivity analysis using imputed values confirmed that WHELD conferred a statistically significant benefit in DEMQOL proxy (1.5 SEM 0.06 point benefit, Z 2.50, p=0.015), CMAI (1.96 SEM 0.08 point benefit, Z=2.06, p=0.04) and NPI (Mean Difference -2.45 SEM 0.066 Z=2.64 P=0.01) compared to treatment as usual.

Adverse Events

A total of 549 Serious Adverse Events were recorded during the period of the trial. The events were balanced between the two treatment groups with no statistical differences (291 events in WHELD group and 258 in TAU group – Table 4). There was no significant difference in mortality between the WHELD and treatment as usual group (Relative Risk 1.08 95% CI 0.86 to 1.35, P = 0.50).

Table 4: Serious Adverse Event reporting by category and WHELD treatment group

	Group		
SAE category	**WHELD**	**TAU**	**TOTAL**
Dehydration	8	2	**10**
Fall	30	14	**44**
Fractures	15	13	**28**
Mortality	122	103	**225**
Pneumonia	16	12	**28**
Stroke	3	8	**11**
Delirium	0	1	**1**

Chest Infections	26	15	**41**
Renal	2	1	**3**
Increased confusion	4	0	**4**
UTI	11	7	**18**
Pulmonary embolism	1	0	**1**
Other	53	82	**135**
Total per group	291	258	**549**

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485 *Cost analysis*

486 The direct cost of delivering the intervention compared to TAU was £8,627 per home. 53%
487 (£4,554) of the cost related to WHELD Champion time spent in training and supervision. The
488 remaining costs related to therapist time. Delivery of the intervention to residents incurred
489 an additional £130 per person per month. The additional cost incurred for AR was £23 per
490 resident, which accounted for Champion time spent reviewing antipsychotic use in 16% of
491 residents and contacting prescribing physicians. Analysis of service use showed higher
492 healthcare costs unrelated to the intervention in the TAU group compared to the WHELD
493 intervention group. Participants receiving the intervention showed a significant health and
494 social care cost advantage. Taking into account the cost of the intervention and the total
495 health and social care costs, there was a cost advantage for the WHELD treatment (Table 5).

496

497

Table 5 Unadjusted mean costs and mean cost differences at baseline and over nine months (£, 2014 – 2015)

	Intervention		TAU		Intervention vs. TAU^	
Cost categories	Mean (£)	SD (£)	Mean (£)	SD (£)	Unadjusted mean difference (£)	95% CI
WHELD intervention	2713	121	0	-	2713	(2701 to 2724)
Baseline (n=887)						
Accommodation charges	9480	(2010)	10233	(3675)	-753	(-1128 to -365)
Hospital	387	(1759)	407	(2413)	-20	(283 to 242)
Primary care	96	(126)	98	(148)	-2	(19 to 14)
Community health	23	(80)	19	(79)	4	(-7 to 14)
Emergency	12	(37)	9	(34)	3	(-1 to 7)
Total health and social care costs	9998	(2601)	10766	(4396)	-768	(-1249 to -338)
Nine month follow-up (n=553)						
Accommodation charges	28606	(10863)	33005	(12428)	-4399	(-5725 to -2898)
Hospital	269	(1166)	262	(1267)	7	(-183 to 188)
Primary care	700	(294)	1020	(301)	-320	(-364 to -277)
Community health	78	(260)	70	(206)	8	(-23 to 44)
Emergency	49	(133)	85	(244)	-36	(-68 to -10)
Total health and social care costs	29702	(8774)	34442	(11106)	-4740	(-6129 to -3156)

^ Cost comparisons for nine months include covariates for site, age, baseline CMAI score and baseline value of the same cost variable.

Baseline cost comparisons include covariates for site, age and baseline CMAI score

Discussion

In what is, to our knowledge, the largest RCT conducted of a staff training and non-pharmacological intervention for people with dementia living in nursing homes, we have demonstrated that the WHELD intervention confers a statistically significant improvement in QoL over nine months. There was also a statistically significant benefit to agitation and overall neuropsychiatric symptoms over the nine-month period. Whilst the effect size was small, the benefits in agitation and neuropsychiatric symptoms are comparable to (agitation) or better than (NPI) the benefits seen with antipsychotic drugs. There was also a significant increase in the proportion of positive care interactions between care staff and residents with dementia with a moderate effect size. Importantly, the benefits were achieved in the context of a cost saving and used a model that can readily be implemented into nursing homes. Antipsychotic drug prescribing was stable in both treatment groups across the study and the WHELD treatment intervention did not reduce antipsychotic use, albeit from a very low baseline frequency.

Despite the importance of QoL few trials have examined impact of interventions on this outcome, This was, to our knowledge, the largest RCT conducted of a staff training and non-pharmacological intervention for people with dementia living in nursing homes. The WHELD intervention conferred a statistically significant improvement in QoL over nine months, building on a previous proof-of-concept study of WHELD. That study reported a reduction in QoL following antipsychotic review which was mediated by social interaction within the context of an overall person-centered care training paradigm for care staff [9]. We would speculate that the added benefit was probably a reflection of the structured approach to promoting pleasant activities involving social interaction, The optimization of the WHELD intervention has maintained benefit but reduced overall cost, making it a cost-effective

program for delivery in care homes. A sub-group analysis focusing on people with mild-moderate, moderately severe and severe dementia indicated that benefits on quality of life were more robust in people with moderately severe dementia.

Agitation is a frequent and distressing symptom for people with dementia living in nursing homes [10,11,41]. Benefits from pharmacological treatment with atypical antipsychotics are limited to modest improvements in aggression [12,13,15], and the significant advantage on the CMAI compared to control for the WHELD intervention is comparable with the modest treatment advantage for atypical antipsychotics from a meta-analysis of previous RCTs [12,13,15]. In addition, the use of atypical antipsychotics is limited by the significant adverse effects of these medications in people with dementia [12,13,15]. Although recent studies have begun to suggest that other pharmacological therapies such as citalopram[20] and dextromethorphan [21] may confer significant benefit for the treatment of agitation, but further studies are needed. There was also a statistically significant benefit in overall neuropsychiatric symptoms conferred by the WHELD intervention compared to TAU, suggesting a breadth of benefit beyond just agitation.

Although comparable to atypical antipsychotics the standardized effects sizes of benefit are small in the context of a clinical intervention. The benefits do however also include benefits in quality of life, which have not been demonstrated with pharmacological interventions. Although there is no established threshold for a clinically meaningful benefit in quality of life, any statistically significant benefit is important given the absence of any benefit in previous studies. In addition, the intervention was not just delivered to a people with clinically significant neuropsychiatric symptom, but conferred benefit amongst a broader population

554 of people with dementia living in care homes. Whilst the effect size would be considered
555 marginal in terms of a clinically significant benefit, we believe that the benefits to the broader
556 population of people with dementia in care homes make this a meaningful benefit in the
557 quality of care.
558
559 This study is consistent with the evidence base but provides important and novel data within
560 the literature. Our results also compare favorably to the small number of published
561 intervention studies which have focused on promoting person-centered care, none of which
562 have reported benefits to QoL[6,7]. The findings are particularly favorable when compared
563 with trials of antipsychotic medications which show only very modest benefits over 12 weeks
564 in the context of significant harms [42,43]. In addition, the current study shows cost-
565 advantages over usual care, which has not been demonstrated with any previous drug or non-
566 drug interventions.
567
568 Elements of the WHELD intervention, such as social interaction and pleasant events, have
569 previously been demonstrated to improve agitation in modest sized RCTs [22,23].
570 Incorporating them within a coherent framework such as WHELD enables straightforward and
571 affordable implementation of these approaches in clinical and care practice.
572
573 Interestingly, there was a low baseline use of antipsychotic medications (<10%) in this study,
574 reflecting the major changes in clinical practice and the reductions in antipsychotic use that
575 have been achieved for people with dementia in the last decade. In contract to our previous
576 factorial RCT of the WHELD intervention, no significant reduction in antipsychotic use was
577 achieved and antipsychotic use was stable in both groups. This is likely attributable to a

578 combination of the low baseline levels of antipsychotic prescription and the more limited
579 education program for primary care physicians within the current study than in the previous
580 factorial RCT, and highlights the potential additional value of primary care education
581 programs in parallel to care home training.
582
583 This study is a robust well powered RCT evaluating the sustained impact of combining person-
584 centered care and evidence-based non-pharmacological interventions for people with
585 dementia in nursing homes. The study had good retention of surviving participants compared
586 to most studies conducted in nursing home settings. The intervention evaluated was
587 pragmatic, fully manualized and designed so that it can be easily disseminated and
588 implemented in routine clinical practice. There were also limitations. Antipsychotic review
589 was based on augmenting processes within care homes to trigger medical review and did not
590 in this study involve proactive primary care education. In addition, although the study used a
591 well validated method, evaluating quality of life in people with dementia is challenging and
592 all methods have some limitations. High mortality rates are usual in studies of frail groups of
593 individuals living in care homes, but lead to high non-completion rates and present some
594 challenges for data analysis and interpretation. One of the original secondary outcomes was
595 to evaluate the impact of the intervention on the care home environment. The selected scale
596 focused mainly on the physical building rather than other aspects of the environment, and
597 the Program Management Group therefore decided to omit this measure at 9 month follow-
598 up as it was unlikely substantial building renovations had taken place in any of the
599 participating care homes.
600

A key issue for future studies is the sustainability of the intervention, particularly with turnover of staff including the dementia champions. To be sustainable the WHELD intervention needs to be firmly embedded within the care home culture, and it will be important for further research to identify the optimal approach to maintain benefits. As WHELD is largely verbally based, it will also be important to further evolve interventions more tailored to the needs of people with more severe dementia.

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743 **Supporting Information Legends**

744 **S1 Text:** CONSORT Chart showing flow of participants through the none-month study. 847

745 participants were randomized, of whom 757 were included in the full imputation analysys

746 **S2 Text:** Data analysis protocol for the randomized controlled trial, as developed for this study

747 and the associated factorial study [25]

748 **S1 Table:** Summary and Examples of WHELD Training

Fig 1

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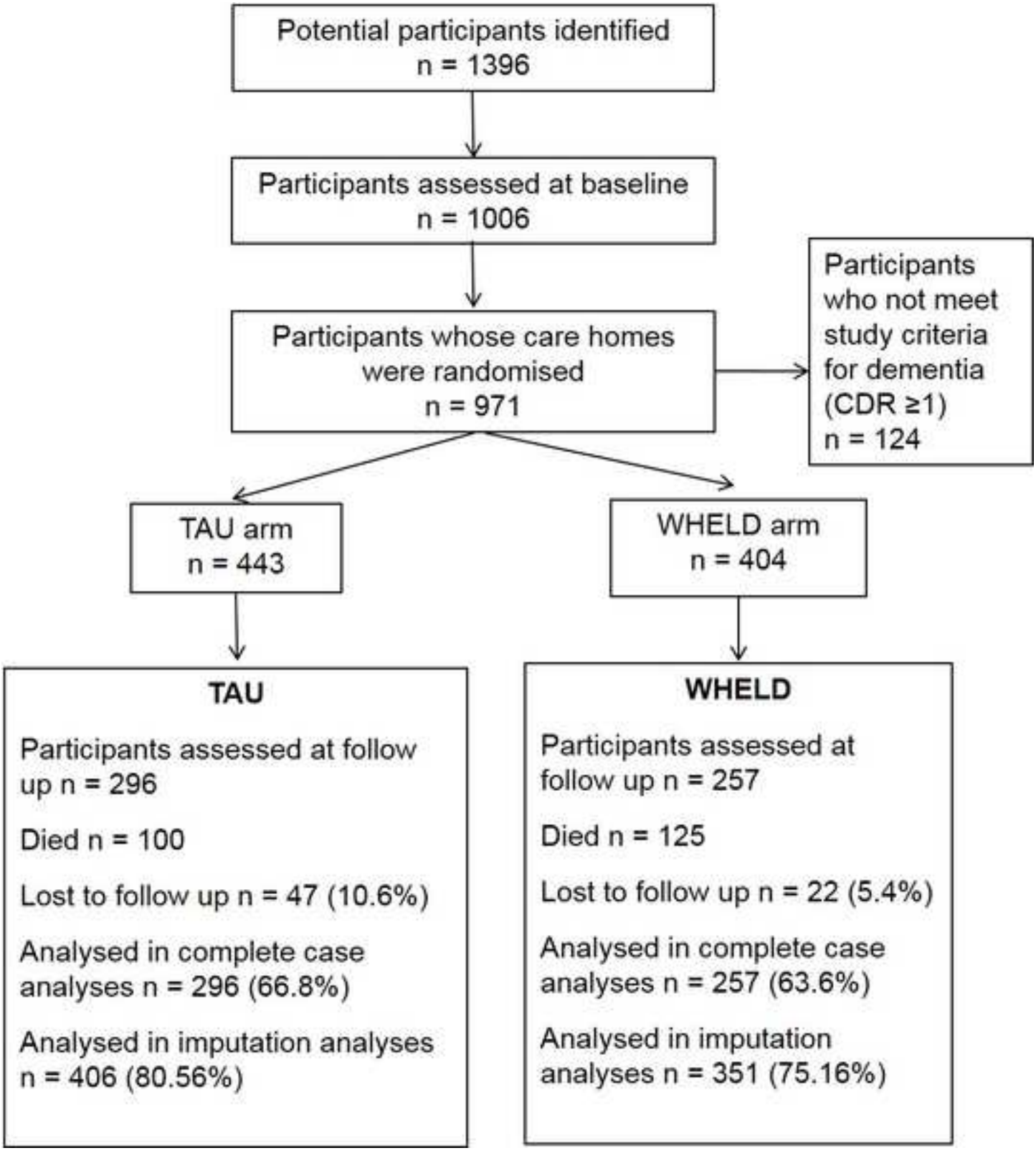

S1 Table

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Supporting Information

S1_Table.docx

CONSORT Checklist

CONSORT Diagram

Ethics Approval Letter 1

Ethics Approval Letter 2 (Final Approval)